The Significance of Splenomegaly in Cirrhosis of the Liver *

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IN A RECENT report [27] we called attention to the fact that in the portal vein of anesthetized dogs and humans the level of oxygen saturation was approximately 30 per cent higher than that in the inferior vena cava below the entrance of the renal veins. It was demonstrated that this phenomenon was due to the existence of normally occurring arteriovenous anastomoses which on occasion allowed arterial blood to bypass the capillary bed to an area and empty its highly saturated blood directly into the venous system.

In a series of detailed observations [20] limited to the upper stomach where mucosal function could be correlated with blood supply, the opening and closing of this sluice-like mechanism was noted to be phasic with function. With histamine injection and vagal stimulation there was an increase in portal and splenic venous pressure with no change or a slight fall in oxygen saturation and an increase in the output of hydrochloric acid. Direct flow determinations were not made at this time. When epinephrine was given, however, there was a considerable rise in portal and splenic venous pressure often to levels twice that seen in the control animal. At the same time the oxygen saturation tended to equal that noted in the artery. The secretion of hydrochloric acid was depressed. When histamine was given in amounts sufficient to induce severe hypotension, there was a fall in both portal and splenic venous pressure. A considerable fall in portal and splenic oxygen saturation was also noted and acid secretion was absent.

We interpreted these findings as demonstrating that when hydrochloric acid is secreted by the stomach, the energy requirements are so great that increased blood flow through the stomach with increased perfusion through the mucosal capillary bed is essential. When acid is not being secreted much of the capillary bed in the mucosa is closed and the arterial blood shunted directly into the veins by means of arteriovenous anastomoses in the gastric submucosa.

From these studies it was postulated that in any of the structures of the body where function is phasic, such a circulatory mechanism would be essential. It was further postulated that the control of the sphincteric arrangement of vascular musculature responsible for blood flow through or around arteriovenous shunts, was humoral in view of the fact that certain substances normally present in the circulation could affect it. There would in all probability be other substances as well. This mechanism would also be sensitive to the integrity of hepatic cellular function in either the formation or the degradation of substances serving as such humoral stimuli. Such a postulation was made on the basis that known substances that had proved to be active at such sphincter sites are also known to be modified by liver function.

The control of this mechanism becomes important in the consideration of abnormalities that might result from its distortion. We have already referred to the fact that venous blood returning to the hemiazygous from the terminal esophagus in patients with cirrhosis of the liver and esophageal varicosities, is highly saturated with oxygen reaching almost arterial levels and that one must consider the cause of

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such varicosities therefore in another light than that of pure venous obstruction. It will thus be of value to study the vascular system in other areas of the body in patients with cirrhosis of the liver for evidence of similar abnormalities.

Observations of others suggest that a vascular bed abnormality in cirrhosis may be fairly widespread. That there is as a rule a hyperkinetic circulation is a common clinical observation. Tachycardia is often noted and even a capillary pulsation may at times be seen. Warm and flushed extremities denote increased peripheral blood flow and one can often note an active precordial thrust. Erythematous palms (liver palms) and soles are so frequent as to form part of the clinical syndrome of cirrhosis. In a like manner the focal telangiectatic formations in the skin (vascular spiders) that also are frequently described in the cirrhotic patient can be easily demonstrated to be abnormal arteriovenous connections.

Patients with cirrhosis with well established morphologic abnormalities are generally acutely ill when they are admitted to a hospital and there are not too many well reported laboratory studies of the circulatory state. Some of them, however, are significant. In 1953, Kowalski and Abelman [12] reported that approximately a third of the patients with Laennec's cirrhosis studied at rest, exhibited a cardiac output that was increased out of proportion to the oxygen consumption. In a subsequent study [1] observations were made following exercise. These observers noted that the cardiac output during exercise in their subjects was increased without a corresponding increase in oxygen consumption, resulting in a narrowing of the arteriovenous oxygen difference. Again elevation of the resting cardiac output was associated with a lowering of the peripheral vascular resistance in these studies. They considered their findings as indicative of peripheral vascular dilatation analogous to multiple arteriovenous shunts in parallel. Interestingly enough almost similar figures as those obtained in cirrhotics were also found in patients with chronic alcoholism.

In a patient with subacute hepatitis and liver failure who presented no evidence of portal collateral circulation at autopsy, Hecker and Sherlock [10] noted similar elevations of the cardiac output. In a similar patient with fulminating hepatitis and without a change in blood pH there was a cardiac output of 15 L./min. with normal blood volume and considerably lowered peripheral vascular resistance.[17] The highest cardiac output that we have observed in any of our patients with cirrhosis coming to operation has been 17 L./min. at rest. An increase in peripheral blood flow in patients with cirrhosis was noted by Abramson and Lichtman,[2] later by Martini and Hagemann.[16]

The tendency of patients with cirrhosis to develop a lowered arterial oxygen saturation has been the subject of recent study. This was first noted by Snell [24] and later by Keys and Snell.[11] They found such a decrease in saturation in 48 of 61 patients studied. Subsequent reports have confirmed this observation but the frequency in which it has been encountered is somewhat less. In a recent excellent contribution [9] this lowered arterial saturation was related to the presence of veno-arterial shunts. It was demonstrated that flow through the shunts averaged 9.5 per cent of the cardiac output and 12 of 19 patients studied were found to be above the 6 per cent that is regarded as the upper limit of the normal value with the technic that was used.

In 1956, Rydell and Hoffdauer [23] described a patient with "juvenile cirrhosis" who was followed for a number of years and who presented cyanosis, clubbing of the fingers and eventual cardiac failure. Clinical studies revealed a very high cardiac output with no intracardiac shunt, normal respiratory function and the presence of a physiologic intrapulmonary vascular shunt estimated at 40 per cent of

the cardiac output. The shunt could not be identified on roentgenograms or by lung biopsy specimens taken at operation. Even at necropsy there was no gross or microscopic abnormality noted. Injection of the blood vessels of the right lung revealed, however, that there were numerous widespread vascular channels that connected directly and indirectly the pulmonary arteries and veins. Cyanosis and clubbing of the fingers is not an unusual finding in children with cirrhosis and was described by Fluckiger [8] as early as 1884. The existence of anastomatic channels between the bronchial artery and pulmonary vein of considerable size were described by Tobin and Zariquiery [25] who were able to pass glass beads 500 micra in diameter through the artery into the vein. Also demonstrated have been thoracic anastomoses between the portal and pulmonary circulations.[6] Other observations confirm the tendency to arterial unsaturation and tend to explain it on the basis of functioning communications between arterial and venous systems in the lungs, the azygous veins and perhaps other parts of the body.[22, 26]

There is an increase in the plasma volume in Laennec's cirrhosis, an average increase of more than 10 per cent above the predicted normal having been observed.[18] An increase in blood volume has also been reported and correlated with a possible collateral circulation between the portal vein and the systemic circulation.[7] Such alterations in plasma volume and red cell mass may tend to obscure the true hematologic picture, especially since frequently the increase in plasma is relatively greater than that in red cell mass suggesting a more severe degree of anemia than may actually exist. This may explain at times the relatively poor response to anti-anemic agents.[4]

Another complicating feature of the blood picture is the factor of a considerable decrease in the half-life of red cells in patients with cirrhosis. Allen *et al.*[3] have estimated the red blood cell half-life to be between 21 and 37 days in a series of patients studied and noted also that such patients were more likely to have an indirect serum bilirubin value of 1.8 mg./100 ml. or above along with an elevated corpuscular hemoglobin level. These findings may possibly be the explanation for the relative increase in plasma over red cell mass and why patients with cirrhosis of the liver do not as a rule have overt evidence of polycythemia. Murray *et al.*[17] have studied these phenomena in the same patients along with controls and correlated them. As might be anticipated an increase in blood volume was found in those patients who had an increased cardiac output, arterial desaturation, and low serum albumin levels.

In the present study we shall be concerned with the problem of splenomegaly in cirrhosis of the liver. This is almost a constant finding, indeed even at times preceding fibrotic changes in the liver, and thus an investigation into the mechanism of this enlargement of the spleen may provide some information about the over all problem of therapy. In particular have we concerned ourselves with blood-flow through the spleen. Much of the information needed could not reasonably be obtained from human studies and the dog therefore has been used as the experimental animal. This has been done with full realization of the problem created when the spleen of one species is compared to that of another. Where these differences have been apparent adjustments in interpretation have been made.

Methods

1. Determination of the effect of occlusion of the splenic vein on splenic arterial flow, splenic venous pressure and splenic size.

The blood supply to the dog's spleen is more compartmentalized than is that of the human. There is also a more extensive collateral circulation to the epiploic veins. These were all ligated carefully in contiguity before the main splenic vein was

occluded, care being taken not to injure the arterial supply.

Pentobarbital 35 mg./Kg. was used as the anesthetic agent as it was found that this consistently produced splenic engorgement and all spleens at operation were reasonably near the same size. An endotracheal tube was introduced and constant ventilation obtained by the use of a Starling pump. A midline laparotomy incision was used. Splenic arterial and venous blood flow were measured with a square wave electromagnetic flowmeter * using a 7.5-mm. probe. The probe was calibrated with known rate of blood flow after the procedures were performed. Because of the sensitivity of the splenic nerves to manipulation and to temperature change, this plexus was blocked with procaine during flow determinations. The temperature in the abdomen was maintained by using heated saline and from the heat generated by the probe which had to be held manually during the determinations. A polyethylene catheter was placed in an epiploic vein and connected to a Statham strain gauge manometer and the pressure continuously recorded on an Offner oscillograph.

Splenic size was measured in terms of length. This was found to be more consistent than either width or thickness or a combination of these.

2. Splenic flow with the spleen enlarged and during splenic contraction.

Splenic enlargement was obtained by the use of pentobarbital anesthesia. Splenic contraction was obtained by the use of norepinephrine (Levophed®) given by constant intravenous injection .02–.04 mg./kg./min. or as a comparable single dose.

3. Evidence of arteriovenous shunts in the dog's spleen.

On whole blood samples obtained from the catheter in an epiploic vein threaded into the splenic vein and from another in the femoral artery, oxygen saturations were determined by a modification of the method of Holling *et al.* or with the Waters Double Scale oximeter. These determinations were done during splenic engorgement induced by pentobarbital anesthesia and after contraction resulting from injection of .02–.04 mg./kg. of norepinephrine.

Following extirpation of dogs' spleens in both the distended and contracted states, a cannula was placed in the splenic artery and another in the splenic vein. The artery was perfused at a pressure of 150 mm. of mercury with sodium citrate to prevent clotting and this was followed with water to produce hemolysis. Such perfusion was difficult or even impossible in many of the distended spleens but done with ease in the contracted viscera. Small glass beads ranging in size from 25 to 600 micra were now injected. These were recovered from the splenic vein by passing the perfusant through a 25 micra mesh stainless steel filter. **

Using the same technic as above, the spleen was cleared of blood, perfused with acetone, and the splenic artery and vein injected simultaneously with 12 per cent vinyl plastic in acetone after the method of Narat *et al.*[18] as modified by Liebow *et al.*[15] A pressure of approximately 175 mm. of mercury was used both for the artery and the vein as it was found that the viscosity of the material was such as to make perfusion difficult at lower levels. At no time was a vessel smaller than 25 micra noted to contain any of the plastic material and it was extremely rare to find branches this small. The specimens were digested in concentrated hydrochloric acid and cleared in 10 per cent formalin.

Before the injection of vinyl plastic in both dog spleens and in human spleens removed at operation or at autopsy the viscus was perfused when indicated with norepinephrine.

* Carolina Medical Electronics, Winston-Salem, North Carolina.

** Pyramid Screen Company, Brookline, Massachusetts.

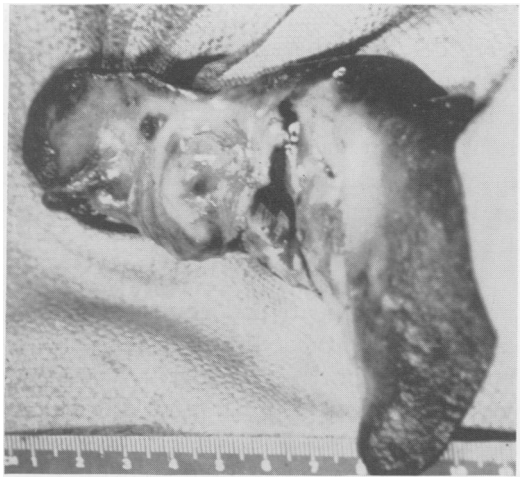

FIG. 1. Dog spleen three months after ligation of the splenic veins. Note the considerable decrease in size, the deposit of organized fibrin on the anterior surface and the tear in the capsule where it was separated from adherence to the anterior abdominal wall.

Results

1. Splenic arterial flow as might be anticipated was closely related to splenic venous flow. Immediately following ligation of the splenic vein in dogs the spleen would increase in length from 25 to 35 cm., and the venous pressure from 10 to 50 mm. of mercury. As equilibrium was established a decrease in arterial flow became apparent. The spleen was inspected at laparotomy at intervals for the first month and gradual decrease in splenic pressure and splenic size noted. At the end of three months the spleen was small and soft, having relatively little flow. A characteristic decrease in size was from 37 cm. in length to 10 cm., and a venous pressure of 12 mm. of mercury (Fig. 1).

The compartmentalization of the dog's spleen was utilized to demonstrate the relationship between inflow and outflow. The venous radicles from the lower pole of the spleen were ligated and norepinephrine injected in the cephalic vein. That portion of the spleen drained by these radicles failed to contract appreciably, suggesting that little of the norepinephrine had entered this part of the spleen (Fig. 2).

On several occasions upon re-examination of the spleen it was noted to be about normal in size. At such times it was apparent that incomplete ligation of many of the small splenic branches had not been carried out. These had enlarged and were noted to be carrying blood from the spleen at a slightly higher flow than normal.

Figure 3 illustrates a characteristic change in arterial flow following temporary occlusion of the splenic vein. Before occlusion the blood flow is calculated at

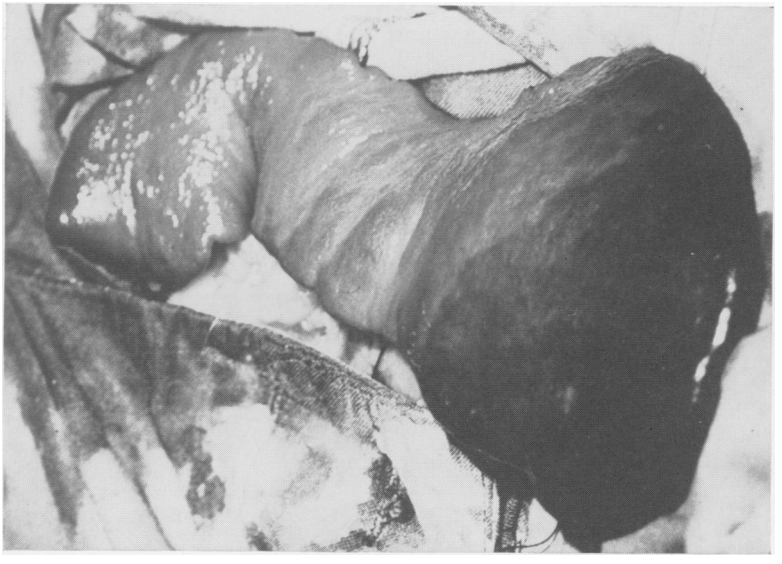

FIG. 2. Dog spleen with vein to lower pole ligated. Norepinephrine has been given intravenously. Note the darker color of the lower pole as compared to the remainder of the spleen and its failure to contract.

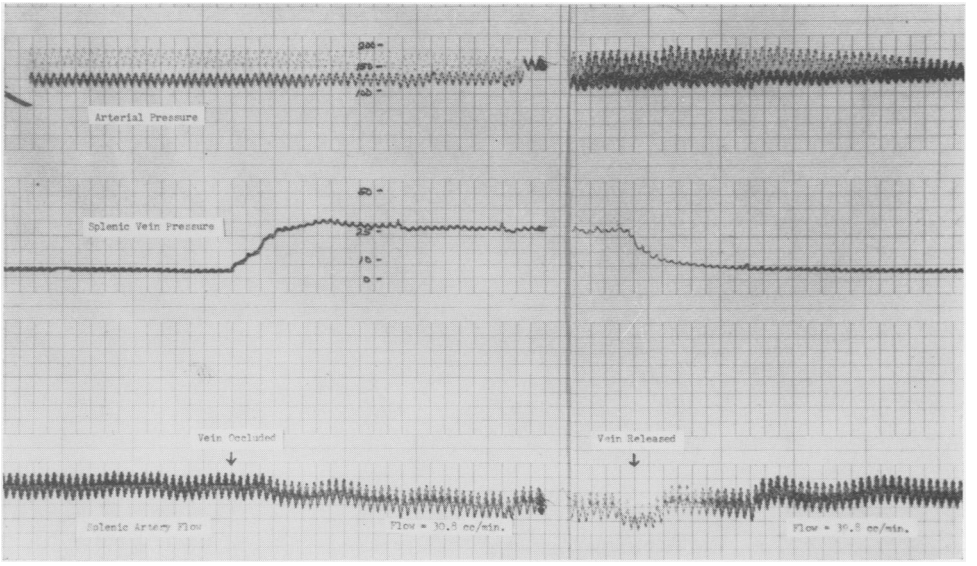

FIG. 3. Determination of the effect of occlusion of the splenic vein on splenic artery flow, splenic vein pressure and arterial pressure. Determination of flow made by use of square wave electromagnetic flowmeter.

39 ml./min. Following occlusion the flow falls approximately 25 per cent to 30.8 ml./min. After release of the occlusion the flow returns to a slightly higher rate than normal, 39.8 ml./min. and then slowly adjusts to control rate. If all the collateral channels for venous flow are occluded this change is even more striking (Table 1).

Under the conditions of this experiment then, obstruction of the splenic vein results in initial splenomegaly and elevation of splenic venous pressure which is followed shortly by a decrease in splenic size to well below that of normal, the decrease in size being in inverse proportion to the collaterals established. There is also a de-

TABLE 1. *Effect Occlusion of Splenic Vein on Splenic Arterial Flow*

		Splenic Vein Not Occluded			Occlusion of Splenic Vein		
		Femoral Arterial Pressure, 6 mm. Hg	Splenic Venous Pressure, mm. Hg.	Splenic Arterial Flow, cc./min.	Femoral Arterial Pressure, mm. Hg	Splenic Venous Pressure, mm. Hg.	Splenic Arterial Flow, cc./min.
Dog. 1	(1)	200/125	5	40.16	200/125	50	36
	(2)	200/120	13.7	32.2	180/110	50	30
	(3)	180/110	5	33.8	180/110	25	30.8
	(4)	a. 175/110	5	39.8	175/110	23.5	25.2
		b. 180/110	5	33.4			
Dog 3 18.2 kg.	(1)	125/75	15	111.0	a. 125/75	35	88.8
					b. 125/75*	35	93
	(2)	125/75	7	112.0			
	(3)	a. 115/75†	12	97	100/65	50	46
		b. 115/75	10	86			

Each number represents a repeat of control and occlusion.

* 4 min. of occlusion.

† All collateral venous drainage divided when splenic vein occluded. A much more abrupt rise pressure fall in flow noted.

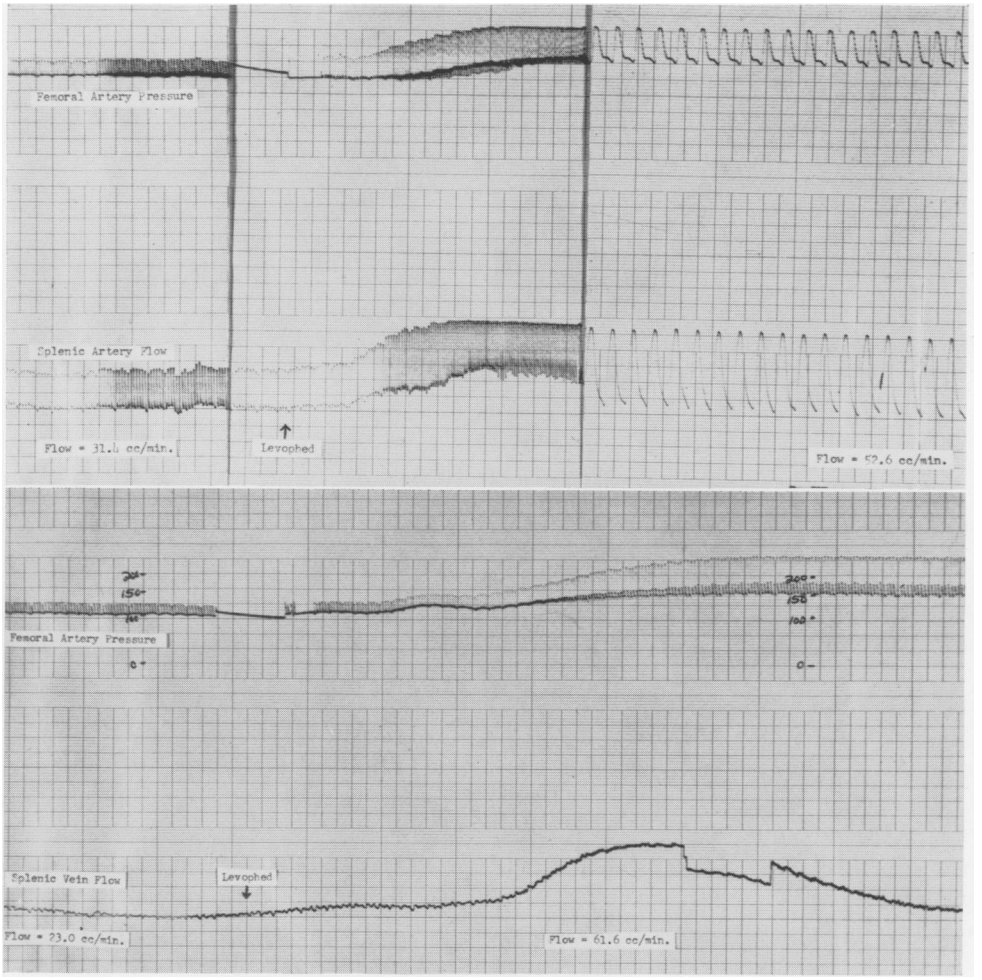

FIG. 4. (Top) Effect of norepinephrine on splenic artery flow. (Bottom) Effect of norepinephrine on splenic venous flow.

crease in splenic arterial flow and an increase splenic venous pressure in proportion to the degree of obstruction.

2. It has been noted previously that the dog's spleen contracts upon stimulation with epinephrine more violently than does that of the human. We also have observed that when the dog's spleen undergoes such contraction the color changes from a deep purplish-blue to a deep red, in proportion to the decrease in size. It is important to know whether this phenomenon of splenic contraction is associated with a decrease in flow of blood through the viscus or an increase in flow to explain this color difference. It will be noted in Figure 4 that with contraction of the spleen there is an increase in flow through the splenic artery as well as an increase in flow through the splenic vein. The increase in arterial pressure that is noted lasts longer than the effect of the norepinephrine on the spleen itself. This increase in blood flow through the spleen without considerable splenic perfusion is suggestive of the presence of channels connecting arterial and venous flow, bypassing the splenic pulp. It now becomes important to demonstrate the actual presence of such shunts and their position within the splenic vasculature (Table 2).

3. Arteriovenous differences in the

TABLE 2. *Effect of Norepinephrine on Splenic Blood Flow*

		Control			Intra Arterial Injection .04 mg./kg. Nor-epinephrine			
		Femoral Artery Pressure, mm. Hg	Splenic Artery Flow, cc./min.	Splenic Venous Flow, cc./min.	Time After Injection	Femoral Artery Pressure, mm. Hg.	Splenic Artery Flow, cc./min.	Splenic Venous Flow, cc./min.
Dog. 2 13 kg.	(1)	160/125	36		30″	200*/160	52.6	
					2′	200*/150	36	
					10′	175/125	31	
	(2)	125/100		23	1′	200*/150		62
Dog 3 18.2 kg.	(1)	150/100	82			200*/150	118	
					28′	150/100	87	
	(2)	135/85		69	1′	200/150		110

* Control flow was determined on splenic artery. Then norepinephrine injected. After 30 min. rest flowmeter was placed on splenic vein and second injection nor-epinephrine administered.

oxygen saturation of the blood were determined with the spleen engorged and following a single administration of .02 or .04 mg./kg. of norepinephrine. This was correlated with splenic venous pressure. In six such experiments the mean arterial saturation in the control was 98.5 per cent with a splenic venous saturation of 88.8 per cent. The mean arteriovenous saturation difference was 9.7 per cent. Following the administration of norepinephrine the mean arterial saturation was 98.5 per cent and the mean splenic venous saturation was 95.9 per cent, a difference of 2.6 per cent. The mean control splenic venous pressure was 9.2 mm. of mercury, while following the administration of norepinephrine it was 20.7 mm. of mercury. These changes are significant at the 1.0 per cent level. The wide variation in splenic venous pressure has been a fairly consistent feature. This may be considered as evidence of the lability of the portal circulation (Table 3).

The perfusion of the spleen with glass beads has given inconstant results. As has been stated, when catheters were placed in the main splenic artery and vein of a distended spleen and the viscus then remover from the dog, saline perfusion, using ordinary pressures, is difficult. It is rare that we have been able to recover beads

TABLE 3. *Arteriovenous Saturation Differences and Splenic Venous Pressure Changes Following Norepinephrine .04 mg./kg.*

	Control			After Noreinephrine			Rise	
	Arterial O_2 Sat.	Splenic Venous O_2 Sat.	Splenic Venous Pressure, mm. Hg	Arterial O_2 Sat.	Splenic Venous O_2 Sat.	Splenic Venous Pressure, mm. Hg	Splenic Venous O_2 Sat.	Splenic Venous Pressure, mm. Hg
Dog 1	100	85.2	13	97	97	19	11.8	6
2	96.2	87.7	5	100	94	21	6.3	16
3	100	95.0	15	100	100	28	5.0	13
4	100	85.2	13	100	97	24	11.8	11
5	95	87.7	5	94	97	21	9.3	16
6	100	91.9	4	100	90.6	11	1.3	7
Mean	98.5	88.8	9.2	98.5	95.9	20.7	7.2*	11.5†

* Standard deviation 5. Standard deviation of mean 2.08.

† Standard deviation 4.4. Standard deviation of mean 1.83. p for both determinations less 0.01.

larger than 25 micra in diameter under such circumstances. When the spleen is in a contracted state on the other hand, the perfusant passes from artery to vein with ease and beads as large as 440 micra have been recovered. At times smaller size beads ranging from 140 to 220 micra are found in the venous outflow. This suggests a variation in size of the lumen of the arteriovenous connections as well as the fact that at times they can be fairly large. It will be recalled that Prinzmetal *et al.*[21] were able to perfuse the spleen of dogs with beads ranging from 160 to 370 micra. The functional state of the spleen in their experiments is not described.

Injection of the arteries and veins of the dog spleen with vinyl plastic has been difficult relating in particular to the inability to perfuse the arterial tree when the spleen was dilated. When the spleen was in a contracted state following perfusion with norepinephrine, the vinyl plastic that was injected in the splenic artery appeared quickly in the splenic vein, making it difficult to tell one from the other. Here again is suggested the presence of large shunts.

Even the human spleen of normal size removed at operation and at autopsy presents perfusion difficulties insofar as the arterial tree is concerned. Here again recovery was inconstant. In most instances the spleens not intrinsically damaged were obtained at necropsy and were studied usually six or more hours after death. These, therefore, cannot be considered normal insofar as the dynamics of the vascular pattern is concerned. Nevertheless, it is of interest that the arterial tree visualized poorly with plastic injections. The venous bed presented various patterns. At times the terminal venules presented a fine and delicate arborization. At other times the arborization was coarser and ended in a knob-like process. Frequently there was little of the fine arborization pattern, there being instead irregular bulb-like endings at times a millimeter or more in diameter suggesting a direct connection with the pulp space (Fig. 5).

When the artery and vein were injected simultaneously with different colored plastic material fairly large vessels could be seen containing a mixture of the two colors. When one injection was made after the other had begun to harden in several areas one could note fairly large arteriovenous connections. These were usually near the hilum (Fig. 6a, b).

With the technic described we have had the opportunity to study five spleens removed from patients with cirrhosis of the liver. We were immediately impressed with the ease in which they could be perfused. The largest glass beads that we attempted to inject through the splenic artery were 600 micra in diameter and these were recovered from the splenic vein. When the arterial and venous vascular beds were injected with a different colored vinyl plastic, the variation in size from that of the normal was impressive (Fig. 7). Here again was evidence of an increased rather than a decreased blood flow. When the injections were made simultaneously there would be seen frequently large areas of the venous bed, filled with plastic that had been injected into the artery (Fig. 8). In other regions one could note areas of venous distortion (Fig. 9) and trace the origin of arterial connection with the vein. These connections near the hilum did not impress us being related to the arteriovenous thoroughfares in the smaller splenic radicles that have been described by Knisely.[13, 14] Because of the viscosity of the plastic that we used, it is highly unlikely that one would anticipate permeation of this thoroughfare.

These injection and perfusion studies of the spleens that were removed from patients with cirrhosis are in keeping with certain of the clinical findings. In all patients there was splenomegaly. In all patients there was noted to be a thrill in the splenic vein at operation. In all pa-

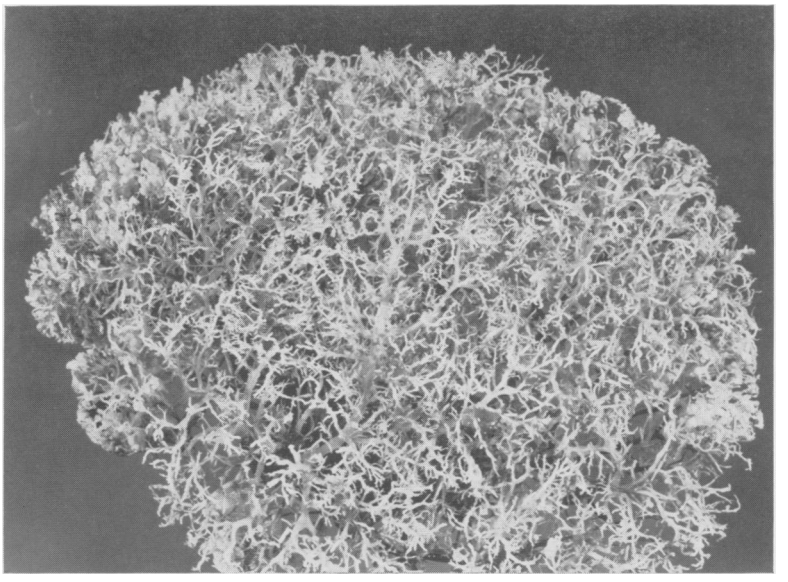

FIG. 5a. Arteriovenous junction in a normal human spleen. The venous injection of vinyl plastic was made after the arterial injection had solidified.

tients the spleen decreased in size when the splenic artery was ligated and the thrill in the splenic vein disappeared. In the two patients studied the oxygen saturation differences between the arterial and splenic venous blood was reduced to 1.9 per cent in one and zero in the other.

Discussion

These studies re-emphasize a physical principle, namely that an appreciable change in the venous outflow from a viscus must reflect itself in the arterial inflow or catastrophe soon supervenes. Thus an increase in arterial inflow must be associated with an increase in venous outflow (if lymphatic interference be excluded) and conversely a decrease in venous flow will be associated with decrease in arterial flow. As we have seen, this principle of reciprocal flow holds in the splenic circulation and splenic vein obstruction cannot *a priori*

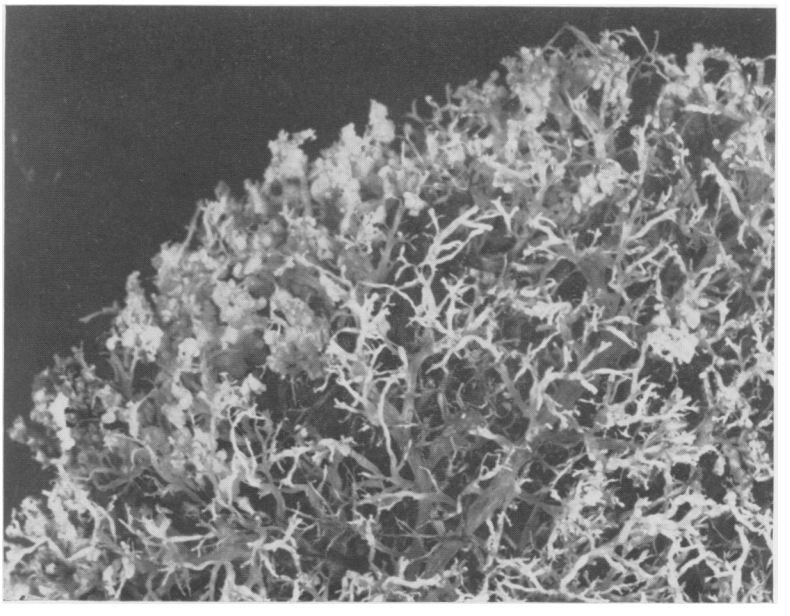

FIG. 5b. Enlargement of area shown in (a).

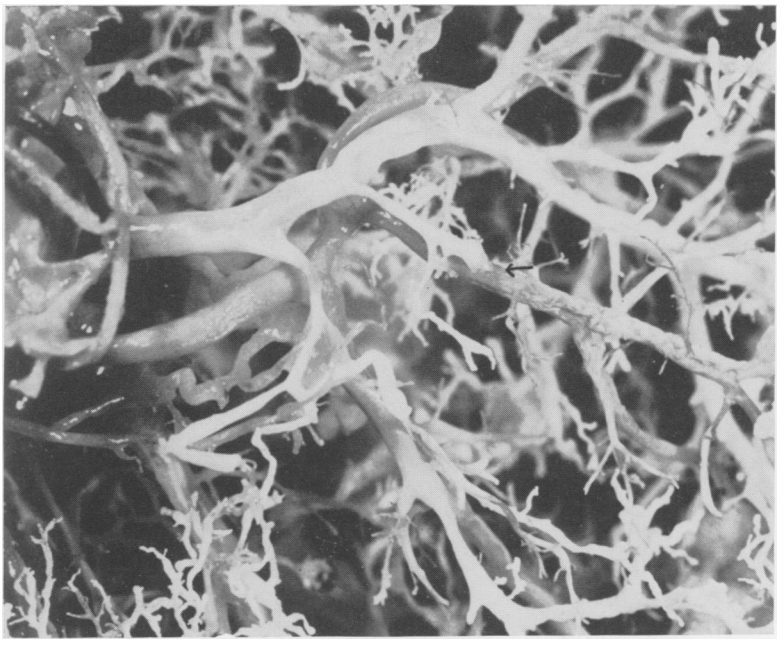

FIG. 6a. Vascular bed of normal spleen. The venous system was injected prior to the arterial. The sparse arterial filling can be noted.

result in permanent splenomegaly. Experimental evidence supports this logical assumption.

These experiments illustrate another important principle, that of phasic bypass. The spleen has an important function of storage of blood and during this period it serves to effect certain changes in the cellular and fluid components of the blood. During time of great energy demand such as violent exercise, however, the spleen discharges its contents into the portal blood stream. During this period of contraction, to a considerable extent the incoming blood from the splenic artery now bypasses the sinusoidal circulation by flowing directly into the splenic vein.

From our studies it seems highly likely

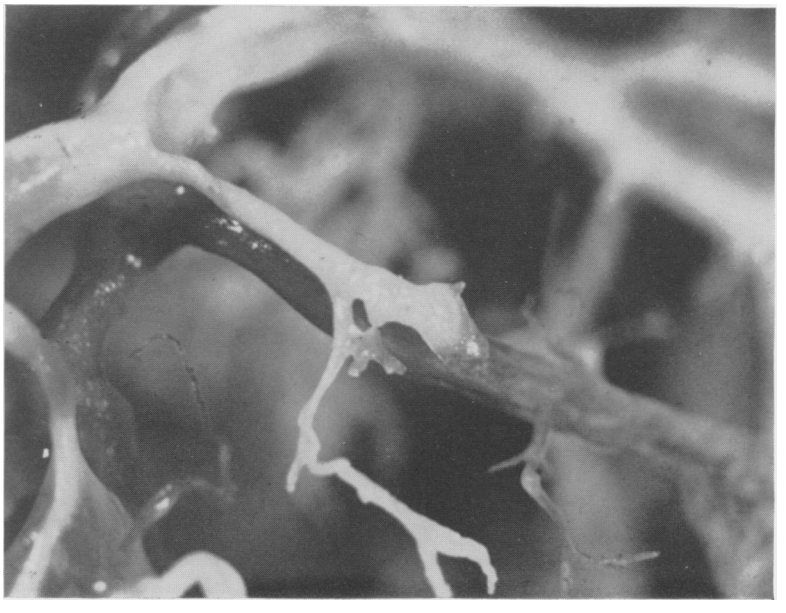

FIG. 6b. Enlargement of margin shown in (a) to illustrate the variation in venous terminals.

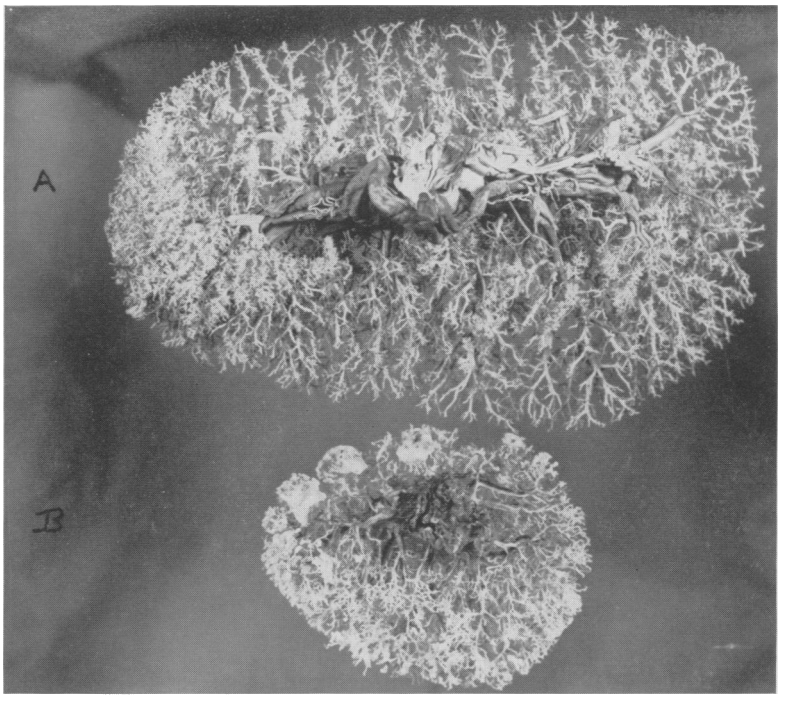

FIG. 7. Vinyl plastic injections of the vascular bed of a spleen removed from a patient with cirrhosis of the liver (a) compared with that of a normal spleen removed at necropsy (b). The veins are white and the arteries dark. The venous injection was made after the arterial injection had solidified and there is no mixing of material. Note the massive vascularity of the spleen in cirrhosis of the liver when compared to the normal one.

that it is this shunting mechanism that becomes altered in patients with certain liver affections such as cirrhosis. As we have seen arteriovenous anastomoses normally present become considerably exaggerated in size and unable to compensate with adequate closure. This is illustrated by the fact that in cirrhosis the spleen is unable to decrease appreciably in size. These anastomoses take place between the arteriole and the venule within the spleen and often near the hilum. Not only is the splenic vein flooded with arterial blood at such times but there will likewise be a tendency toward increase in pressure within the splenic venule with resulting increase in sinusoidal pressure and splenomegaly. It is a well known observation that intrasplenic pressure is usually elevated in patients with cirrhosis of the liver.

The rule of LaPlace ($T = P \times R$) explains the subsequent events.[5] Those veins within the splenic capsule may increase their tension by the advent of the extramural pressure exercised by the splenic capsule and splenic stroma, that is associated with splenomegaly. This increase in tension makes it possible for a comparable increase in intramural venous pressure to occur without an associated increase in the radius of the vein. That portion of the splenic vein outside of the splenic capsule has no such means of increasing the tension in its wall, and the radius thus becomes vulnerable to a change in pressure. This may be prevented at times by the active tension exerted by the smooth muscle in the venous wall but frequently this is unable to compensate. One often notes in cirrhosis therefore long and racemose venous channels in the region of the splenic pedicle. When a radio-opaque substance is injected into the spleen, the flow is so rapid in these large channels that visualization of the splenic vein is lost often before it empties into the portal. This has given a false idea at times of the presence of obstruction.

The resultant diameter of these many large venous channels leaving the spleen is greater than that of a normal splenic vein. The effect is an increase in arterial inflow from the enlarged, tortuous splenic artery usually encountered in cirrhosis. This in-

FIG. 8. Spleen removed from patient with cirrhosis. Note the dark arterial plastic (a) material mixing with the whiter venous plastic (b).

crease in splenic blood flow may be so great that we have on two occasions heard a bruit over the spleen before operation. Quite commonly at operation, as we have noted, there is a thrill palpable in the splenic vein.

This then is the splenomegaly of cirrhosis. The effect of surgical removal we shall leave for another report.

Conclusion

1. In this study we have presented experimental evidence to support the concept that obstruction of the splenic vein produces decrease in splenic arterial inflow. There is initial splenomegaly but the spleen subsequently becomes reduced in size to a degree much smaller than that normally encountered.

2. When the spleen contracts in the normal animal there is an increase in the transport of blood from the splenic artery to the splenic vein. This is associated with a considerable reduction in the difference between the oxygen saturation levels in the artery and vein, and is the result

FIG. 9. Dark plastic material injected into the artery of a spleen removed from a patient with cirrhosis, has entered a vein, discoloring it and distorting it.

of the opening of large arteriovenous anastomoses.

3. A similar pattern of considerable increase in blood flow through the spleen is shown to exist in cirrhosis of the liver. Large arteriovenous anastomoses are demonstrated to be present in the human spleen in cirrhosis and the mechanism in which this produces splenomegaly is described.

References

1. Abelmann, W. H. and H. J. Kowalski: Exercise in Patients with Laennec's Cirrhosis. J. Clin. Investigation, **34**:690, 1955.
2. Abramson, D. I. and S. S. Lichtman: Influences of Ergotamine Tartrate upon Peripheral Blood Flow in Subjects with Liver Disease. Proc. Soc. Exper. Biol. and Med., **37**:262, 1937.
3. Allen, F. A., M. H. Carr and A. P. Klotz: Decreased Red Blood Cell Survival Time in Patients with Portal Cirrhosis. J.A.M.A., **164**:955, 1957.
4. Bateman, Jeanne C., H. M. Shorr and T. Elgvin: Hypervolemic Anemia in Cirrhosis. J. Clin. Investigation, **28**:539, 1949.
5. Burton, A. C. and S. Yamata: Relation between Blood Pressure and Flow in the Human Forearm. J. Appl. Phys., **4**:329, 1951.
6. Calabrasi, P. and W. H. Abelmann: Portocaval and Porto-pulmonary Anastomoses in Laennec's Cirrhosis and in Heart Failure. J. Clin. Investigation, **36**:1257, 1957.
7. Eisenberg, S.: Blood Volume in Patients with Laennec's Cirrhosis of the Liver as Determined by Radioactive Chromium-tagged Red Blood Cells. Am. J. Med., **20**:189, 1956.
8. Flückiger, M.: Vorkamen von Trammelschagelformigen Fingerenphalangen ohne Chronische Veranderungen an der Oder am Herzen. Wien. Med. Wchnschr., **49**:1457, 1884 (quoted by Rydell and Hoffdauer).
9. Georg, J., K. Mellemgaard, N. Tygstrup, and K. Winkler: Venoarterial Shunts in Cirrhosis of the Liver. Lancet, **1**:852, 1960.
10. Hecker, R. and S. Sherlock: Electrolyte and Circulatory Changes in Terminal Liver Failure. Lancet, **2**:1121, 1956.
11. Keys, A. and A. M. Snell: Respiratory Properties of the Arterial Blood in Normal Man and in Patients with Disease of the Liver: Position of the Oxygen Dissociation Curve. J. Clin. Investigation, **17**:59, 1938.
12. Kowalski, H. J. and W. H. Abelmann: The Cardiac Output at Rest in Laennec's Cirrhosis. J. Clin. Investigation, **32**:1025, 1953.
13. Knisely, M. H.: Microscopic Observations of the Circulatory System of Living Traumatized Spleens and of Dying Spleens. Anatom. Record, **65**:131, 1936.
14. Knisely, M. H.: Spleen Studies. 1—Microscopic Observations of the Circulatory System of Living Unstimulated Mammalian Spleens. Anatom. Record, **65**:23, 1936.
15. Liebow, A. A., M. R. Hales, G. E. Lindskog and W. E. Bloomer: Plastic Demonstrations of Pulmonary Pathology. Bul. Internat. Assn. Med. Museums, **27**:116, 1947.
16. Martini, G. A. and J. E. Hagemann: Über Fingernagelveränderungen bei Lebercirrhose als Folge Veränderer Peripherer Durchblutung. Klin. Wchnschr., **34**:25, 1956.
17. Murray, J. F., A. M. Dawson and S. Sherlock: Circulatory Changes in Chronic Liver Disease. Amer. J. Med., **24**:358, 1958.
18. Narat, J. K., J. A. Loof and M. Narat: On the Preparation of Multicolored Corrosion Specimens. Anat. Record, **64**:155, 1955.
19. Parera, G. A.: The Plasma Volume in Laennec's Cirrhosis of the Liver. Ann. Int. Med., **24**:643, 1946.
20. Peters, R. M. and N. A. Womack: Hemodynamics of Gastric Secretion. Ann. Surg., **148**:537, 1958.
21. Prinzmetal, M., E. M. Arnitz, Jr., D. Simkin and H. C. Bergman: Arteriovenous Anastomoses in the Liver, Spleen and Lungs. Amer. J. Anat., **152**:48, 1948.
22. Rodman, T., M. Sobel and H. P. Clone: Arterial Oxygen Unsaturation and the Ventillation Perfusion Defect in Laennec's Cirrhosis. New Eng. J. Med., **263**:73, 1960.
23. Rydell, R. and F. W. Hoffdauer: Multiple Pulmonary Arteriovenous Fistulas in Juvenile Cirrhosis. Am. J. Med., **21**:450, 1956.
24. Snell, A. M.: The Effects of Chronic Disease of the Liver on the Composition and Physicochemical Properties of Blood: Changes in the Serum Proteins, Reduction in Oxygen Saturation of the Arterial Blood. Ann. Int. Med., **9**:690, 1935.
25. Tobin, C. E. and M. O. Zariquiery: Arteriovenous Shunts in the Human Lung. Proc. Soc. Exper. Biol. and Med., **75**:829, 1950.
26. Williams, M. H.: Hypoxemia due to Venous Admixture in Cirrhosis of the Liver. J. Appl. Physiol., **15**:253, 1960.
27. Womack, N. A. and R. M. Peters: An Investigation of the Relationship between Portal Venous Pressure and Inferior Vena Caval and Portal Venous Oxygen Saturation. Ann. Surg., **146**:691, 1957.